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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ANDREW PAUL CHAPMAN and DAVID JOHN KING

Appeal 2008-0454
Application 09/719,045
Technology Center 1600

Decided: May 27, 2008

Before TONI R. SCHEINER, LORA M. GREEN, and
RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 1-10 and 12-15. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The claims are directed to a divalent antibody comprised of two heavy chains linked together by a polymer. The polymer is characterized in the

claim as effective for increasing the circulating half-life of the antibody. Claims 1-10 and 12-15 stand rejected (App. Br. 3) as follows:

1) Claims 1-10, 12, 13, and 15 under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Gonzalez (U.S. Pat. No. 6,025,158, Feb. 15, 2000) (Ans. 4); and

2) Claims 1, 13, and 14 under 35 U.S.C. § 103(a) as obvious over Gonzalez and Barbanti (U.S. Pat. No. 5,436,154, Jul. 25, 1995) (Ans. 6).

Claims 1, 13, and 14 are representative and read as follows:

> 1. A divalent antibody fragment comprising two antibody heavy chains and at least one polymer molecule effective for increasing the circulating half-life of said fragment in covalent linkage, each heavy chain being covalently linked to the other by at least one non-disulphide interchain bridge linking the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue in the other chain, said cysteine residues being located outside of the variable region domain of each chain, characterised in that the at least one non-disulphide interchain bridge contains the at least one covalently linked polymer molecule.
>
> 13. An antibody fragment according to Claim 1 which is able to selectively bind to a cell surface or soluble antigen.
>
> 14. An antibody fragment according to Claim 13 wherein the antigen is human tumour necrosis factor-α or a platelet derived growth factor or a receptor thereof.

REJECTIONS OVER GONZALEZ

Claims 1-10, 12, 13, and 15 stand rejected under 35 U.S.C. § 102(e) as anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Gonzalez.

Claim 1

Claim 1 is directed to a divalent antibody fragment comprising two antibody heavy chains. A polymer molecule which is "effective for increasing the circulating half life" of the antibody is covalently linked to both chains. The claimed antibody has the following additional structural elements:

1) the heavy chains are covalently linked by at least one non-disulphide interchain bridge;

2) the non-disulphide interchain bridge links "the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue in the other chain" (i.e., the sulphur atoms are part of the bridge, but are not directly linked to each other);

3) at least one covalently linked polymer is present in the non-disulphide interchain bridge; and

4) the cysteine residues in the interchain bridge are located outside the variable region domain of each chain.

Scope and content of the prior art

The Examiner finds that Gonzalez describes all the limitations of the claimed antibody, or in the alternative, renders it obvious. The following findings of fact (FF) are pertinent to the Examiner's conclusion that the claimed antibody is not patentable over Gonzalez:

1. Gonzalez describes anti-IL-8 antibodies conjugated to a polymer, such as PEG, which improves the antibody's circulating half life (Gonzalez, Abstract; at col. 27, ll. 12-14; Ans. 5).

2. In its Background section, Gonzalez acknowledges that PEGylation has not been shown to extend the half-life of antibodies in certain prior art

references, but "PEG attached to the sulfhydryl group in the hinge region of a Fab' fragment reduced clearance compared to the parental Fab' molecule" (Gonzalez, at col. 1, ll. 30-43).

3. The antibody can be a monovalent Fab fragment, a monovalent Fab' fragment which includes one or more cysteine residues in the constant region, or an $F(ab')_2$ antibody fragment which has a hinge cysteine between the Fab' fragments (Gonzalez, at col. 11, ll. 57-66; Ans. 5)

4. The conjugates described by Gonzalez "can be made using any suitable technique . . . for derivatizing antibody fragments with polymers. It will be appreciated that the invention is not limited to conjugates utilizing any particular type of linkage between an antibody fragment and a polymer" (Gonzalez, at col. 19, ll. 19-24; Ans. 5).

5. In one embodiment, the polymer can be targeted to the hinge region of the parental antibody fragment, including preferred embodiments in which "a cysteine residue or residues is (are) engineered into the hinge region of the parental antibody fragment in order to couple polymer specifically to a selected location in the hinge region" (Gonzalez, at col. 19, ll. 56-65; at col. 21, ll. 36-40; Ans. 5).

6. For example, Gonzalez teaches linking PEG to the hinge of a Fab' heavy chain, a location which is outside the antibody variable region (Gonzalez, at cols. 120 to 123; particularly, at cols. 122, ll. 64 to 123, l. 3; Ans. 5).

7. Gonzalez also describes conjugates containing a $F(ab')_2$ antibody fragment in which the polymer is attached between the disulphide bridge that would ordinarily link the heavy and lights chains (Gonzalez, at col. 21, 50-59). In this embodiment, the polymer is attached to a cysteine in the light

or heavy chain; the cysteine in the opposite chain is replaced with another amino acid to avoid forming a disulphide bond between the chains (*id.*).

8. In another embodiment, Gonzalez describes antibody conjugates in which "a polymer molecule is used to link together two antibody fragments to form a dumbbell-shaped structure. . . Such structures can be made by using a polymer molecule derivatized with multiple functional groups permitting the direct attachment, or the attachment by means of bi- or multi-functional linkers, of two or more antibody fragments to the polymer backbone" (Gonzalez, at col. 35, ll. 45-57; at col. 41, ll. 41-43; *see* Ans. 5).

Rationale for prior art rejections over Gonzalez

9. The Examiner finds that the teaching in Gonzalez of a polymer molecule linking two antibody fragments together to form a dumbbell-shaped structure (FF 8) coupled to the disclosure of conjugating PEG to the hinge region of an Fab' heavy chain (FF 5, 6) anticipates the structure of the antibody in claim 1 (Ans. 5, 8, 10),

10. i.e., where the heavy chains are linked by a PEG molecule (the "polymer molecule" of claim 1) in an "interchain bridge" formed between the opposing heavy chain cysteine residues (*see Claim 1* above, structural elements 2) and 3)) are in a region outside the variable region domains (*see Claim 1* above, structural element 4)).

11. While there is no single exemplification of the claimed antibody structure, the Examiner finds that the claimed structure is within "the scope of what" Gonzalez teaches because a person of ordinary skill would have been necessarily led to it "among all of the listed possibilities" since "a preferred site of conjugating the polymer to the antibody fragment is at the hinge region" (Ans. 10-11, citing FF 5, 6, 8).

12. In regard to the obviousness of the claimed structure, the Examiner states there are explicit teachings of a dumbbell-shaped structure (FF 8) and a Fab' conjugated to PEG at the hinge region via a cysteine residue (FF 6).
13. Thus, the Examiner asserts, "[t]he only step that one of ordinary skill in the art would need to take is to realize that, when a polymer molecule [is] used to link together two antibody fragments to form a dumbbell-shaped structure, such linkage to each of the two antibody fragments could be formed by the type of coupling chemistry shown at col. 120, line 15-col. 122, line 31" which teaches PEG coupled to the hinge region of the heavy chain of Fab' (Ans. 15).
14. The Examiner finds that such modification would have within the skill of the ordinary artisan since it is one of the explicit and preferred types of coupling/linking chemistry taught by Gonzalez (*id.*).

Obviousness

The "examiner bears the initial burden, on review of the prior art . . , of presenting a prima facie case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). In making an obvious determination, the Examiner must first identity the scope and content of the prior art and then ascertain the differences between the prior art and the claimed invention. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Once the differences between the prior art and the claimed invention have been identified, the next step is to identify a reason why persons of ordinary skill in the art would have been prompted to combine the prior art to have made the claimed invention. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007).

In this case, the Examiner acknowledges there is no specific example of an antibody having the claimed antibody structure comprising a polymer that links cysteine residues, in an interchain bridge, of two opposing heavy chains as required by claim 1 (FF 11). However, the Examiner finds Gonzalez teaches a dumbbell-shaped antibody structure comprised of two monovalent Fab' fragments (FF 8, 12) and describes linking them via a polymer molecule (FF 8). The Examiner also finds that conjugating a polymer molecule to a hinge cysteine residue is a preferred embodiment (FF 5, 6, 11). Based on these teachings, the Examiner contends that it would have been obvious to have formed the dumbbell-shaped antibody by linking the Fab' fragments via the hinge cysteine-polymer structure, meeting the limitations of the claimed interchain bridge.

Appellants contend that the Examiner erred. They assert that Gonzalez teaches away from the claimed antibody because Gonzalez "specifically discusses attaching polymer molecules to a cysteine residue on one chain of a divalent antibody fragment" and substituting the "corresponding cysteine residue in the opposite chain" with another amino acid (App. Br. 6; Reply Br. 5-6; *see* FF 7). Thus, Appellants argue that Gonzalez would have led persons of ordinary skill in the art away from the claimed antibody structure comprising an interchain bridge which links "the sulphur atom of a cysteine residue in one to the chain to the sulphur atom of a cysteine residue in the other chain."

The Examiner has the better argument. Gonzalez explicitly states that antibody conjugates can be produced used any suitable technique and are not limited to "any particular type of linkage between an antibody fragment and a polymer" (FF 4; Gonzalez, at col. 19, ll. 19-24; *see* Ans. 5). Thus, while

Gonzalez describes $F(ab')_2$ antibodies in which the polymer is linked between light and heavy chains – with only one cysteine residue between them (FF 7) – we do not find that this "teaches away" from the claimed invention because Gonzalez expressly states that its conjugates are not limited to a particular linkage type (FF 4).

Gonzalez describes at least two distinct embodiments of divalent antibodies. First, Gonzalez describes a divalent antibody in which the polymer is linked between light and heavy chains and only one cysteine residue is present (FF 7; App. Br. 6). However, Gonzalez expressly describes another antibody structure in which "a polymer molecule is used to link together two antibody fragments to form a dumbbell-shaped structure" (FF 8; Gonzalez, col. 35, ll. 45-57; *see* Ans. 5). This second antibody type is clearly an alternative to the first since Gonzalez states that the polymer joins the two fragments together (FF 8), rather than having the polymer hold the heavy and light chains together as for the $F(ab')_2$ described in column 21 (FF 7). Thus, the only issue – as recognized by the Examiner – is whether persons of skill in the art would have had reason to join the fragments together using a polymer linked to the hinge cysteine residue (FF 13). We agree with the Examiner that Gonzalez would have led to this structure because of the preference for a polymer in the hinge region (FF 2, 5, 13).

In its Background section, Gonzalez refers to prior art which established that "PEG attached to the sulfhydryl group in the hinge region of a Fab' fragment reduced clearance compared to the parental Fab' molecule" (FF 2; Gonzalez, at col. 1, ll. 30-43). Consistent with this, Gonzalez also discloses attachment of a polymer to the hinge region (FF 5), and as pointed out by the Examiner, provides a complete working example in which a

polymer (PEG) is coupled to the cysteine of the heavy chain hinge region (FF 6, 9). Thus, persons of skill in the art would have recognized the advantages of placing PEG in the antibody hinge region.

Appellants' argument fails to acknowledge the dumbbell structure (FF 8) as a distinct and alternative embodiment from the $F(ab')_2$ antibody fragment at column 21, ll. 51-59 (FF 7). Gonzalez does not explicitly teach how to make the dumbbell-shaped structure, but Gonzalez provides clear guideposts, including descriptions of 1) bifunctional linkers to join the antibody fragments to make the dumbbell structure (FF 8); 2) Fab' fragments conjugated to PEG via a cysteine (FF 6); and 3) a teaching that a polymer attached to the hinge region is stable (FF 2). Thus, a likely path a person of ordinary skill would take in making a dumbbell-shaped antibody structure would have been to link the disclosed Fab' fragments at the cysteine residues using the bifunctional linker.

We do not agree that the Examiner relied upon "'hindsight reconstruction to pick and chose among isolated among isolated structures'" (App. Br. 8). Gonzalez's teaching of the dumbbell-shaped structure, without more guidance in how to make it, together with the disclosure of stable Fab' fragments with a polymer conjugated to a cysteine of the hinge region (FF 6), would have suggested to the ordinary skilled person that such Fab' fragments could be readily linked polymer to polymer using a bifunctional linker, as explicitly stated by Gonzalez when characterizing the dumbbell-shaped antibody structure (FF 8).

Precise teachings directed to the specific subject matter of a claim are not required to reach a conclusion of obviousness. *KSR*, 127 S. Ct. at 1741. "[T]he teaching, motivation, or suggestion may be implicit from the prior art

as a whole, rather than expressly stated in the references. . . . The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kahn*, 441 F.3d 977, 987-988 (Fed. Cir. 2006). Here, Gonzalez discloses an embodiment in which two antibody fragments are joined by a bifunctional linker (FF 8). While there is no express teaching in how to make this structure, the knowledge of a person of ordinary skill in the art coupled with the Gonzalez's teachings (i.e., FF 5, 6), would have suggested the claimed structure as a solution to the problem. A "person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR*, 127 S. Ct. 1727 at 1742.

Accordingly, we affirm the rejection of claim 1 as obvious over Gonzalez. Claims 2-10, 12, 13, and 15 fall with claim 1 because separate reasons for their patentability were not provides. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Anticipation

While there is no single exemplification of the claimed antibody structure, the Examiner finds that it is with "the scope of what" Gonzalez teaches because a person of ordinary skill would have been necessarily led to it "among all of the listed possibilities" since "a preferred site of conjugating the polymer to the antibody fragment is at the hinge region" (Ans. 10-11; FF 11). Specifically, the Examiner relies on the following evidence to establish anticipation:

- Gonzalez's teaching of a polymer conjugated to the cysteine of a monovalent Fab' (FF 5, 6)
- Gonzalez's description of a dumbbell shaped structure comprising at least two antibody fragments (FF 8).

The Examiner concludes:

> Gonzalez et al disclose embodiments in which two or more Fab, Fab' or Fab'-SH fragments are covalently conjugated to a polymer backbone. The polymer thus links the antibody fragments. See especially col. 35, lines 40-57 and col. 41, lines 41-62. See col. 35, lines 40-57, wherein there is a teaching of "a polymer molecule used to link together two antibody fragments to form a dumbbell-shaped structure." Such a "dumbbell-shaped structure" is consistent with the divalent antibody fragment of instant claim l.

(Ans. 5).

The Examiner's case boils down to the following assertion: that the claimed antibody structure would necessarily be arrived at when an Fab'-SH fragment is utilized as a starting material to produce Gonzalez's dumbbell shaped divalent antibody structure (*see supra* at p. 11 quoting from Ans. 5).

Anticipation requires that every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim. *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). A specific example is not required to establish anticipation. *See In re Petering*, 301 F.2d 676 (CCPA 1962); *In re Schaumann*, 572 F.2d 312, 316 (CCPA 1978); *Sanofi-Synthelabo v. Apotex Inc.*, 470 F.3d 1368, 1377 (Fed. Cir. 2006). However, when a generic disclosure is the basis for anticipation, one skilled in the art must be able to "at once envisage" the claimed structure in the disclosure. *Petering*, 301 F.2d. at 681.

In our opinion, although Gonzalez suggests the antibody structure of claim 1, too much in the way of mental gymnastics would have been necessary for persons of ordinary skill to have "at once envisage[d]" the claimed antibody structure among the different structures described in the Gonzalez patent.

As pointed out by Appellants, Gonzalez discloses crosslinking the polymer to the antibody through a variety of linkages, including through amino, imino, carboxyl, sulfhydryl, hydroxyl, and other hydrophilic groups (Gonzalez, at col. 41, l. 56 to col. 42, l. 23; *see* Reply Br. 5). Thus, while the sulfhydryl linkage is preferred in the context of a single Fab' fragment, there is the need for picking and choosing among the various possible crosslinking sites to produce a divalent antibody comprised of two Fab' fragments which are linked via a polymer at a hinge cysteine. An anticipatory "reference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972). In this case, because there are a number of different linkages to choose from, we find that the ordinary skilled artisan would not necessarily have envisaged the claimed structure upon reading the Gonzalez patent.

Furthermore, the dumbbell-shaped structure is not precisely defined or described in Gonzalez. Rather, it is open to interpretation and could be read to cover multiple structures, e.g. where the fragments are 1) coupled via the heavy chain cysteine as in claim 1; 2) coupled via their light chains; and 3) coupled via linkages not involving the sulfhydryl group (-SH) of a cysteine

residue. Thus, linkage at the sulfhydryl group is not the only choice for producing a dumbbell-shaped structure.

The Examiner asserts that, when Fab'-SH is utilized to form the dumbbell shape, persons of skill in the art would have "necessarily arrived at" the claimed structure in which the polymer acts as an interchain bridge linking the cysteine residues of each heavy chain (Ans. 11).

We do not agree. On one hand, Gonzalez describes engineering a cysteine residue into the hinge region for the purpose of coupling a polymer (FF 5), but, on the other hand, Gonzalez teaches eliminating one of two cysteine residues when placing the polymer between the heavy and light chains of an $F(ab')_2$ (FF 7). A person of ordinary skill who desired to utilize a hinge cysteine for coupling the polymer would have had the choice of: 1) coupling the polymer to a cysteine on one fragment and a non-cysteine residue on the other antibody fragment (e.g., to avoid forming a disulphide bridge between them (FF 7), or, alternatively, 2) using the hinge cysteine on each Fab' to form an interchain bridge with the polymer molecule. Thus, the determination of whether to use Fab'-SH to form the dumbbell-shaped antibody would entail choosing to use the sulfhydryl group of both Fab' fragments, rather than only one. Once again, picking and choosing would have been necessary to have arrived at the antibody structure of claim 1.

For the foregoing reasons, we do not agree that the antibody structure of claim 1 is anticipated by Gonzalez. We reverse the rejection of claims 1-10, 12, 13, and 15 as anticipated by Gonzalez.

REJECTION OVER GONZALEZ AND BARBANTI

Claims 1, 13, and 14 stand rejected under 35 U.S.C. § 103(a) as obvious over Gonzalez and Barbanti.

Claims 13 is directed to the antibody fragment of claim 1 "which is able to selectively bind to a cell surface or soluble antigen." Claim 14 further define the antigen of clam 13 as "human tumour necrosis factor-α [TNF-alpha] or a platelet derived growth factor or a receptor thereof."

The Examiner finds that Barbanti describes TNF-alpha antibodies for in vivo treatment (Ans. 6). The Examiner finds that persons of skill in the art would have had reason to conjugate these antibodies to PEG for the advantage of extending their half-life as taught in Gonzalez (Ans. 6-7). The Examiner also states that a person of ordinary skill in the art "would have been reasonably motivated to consider both references, because both IL-8 and TNF-alpha are involved in inflammation and because increasing the circulating half-life of an antibody to any mediator of inflammation would have been expected to permit more of the administered antibody to bind the mediator" (Ans. 7).

Appellants contend that 1) Gonzalez does not "provide motivation to couple any antibody fragment to a polymer such as PEG" because it does not generally teach PEG as useful to extend the half-life of any other antibody fragment (App. Br. 10). Appellants also argue that Barbanti 2) "gives absolutely no suggestion that serum half-life is considered to be a problem, or that longer serum half-lives are desired" (*id.*) and that 3) "the Office is focusing upon a single treatment. Barbanti . . . however, clearly contemplates multiple administrations over time" (*id.*).

We are not convinced by these arguments that the Examiner erred. Appellants take the Examiner to task for apparently misquoting Gonzalez's disclosure in column 1, lines 29-31, as teaching that PEG extends the half-life of antibodies, when it actually states that "PEGylation has not been shown to extend serum half-life [of antibodies] to useful levels" (Gonzalez, at col. 1, ll. 29-31; App. Br. 9-10). However, later in the same paragraph, Gonzalez states that "PEG attached to the sulfhydryl group in the hinge region of a Fab' fragment reduced clearance compared to the parental Fab' molecule" (FF 2; Gonzalez, at col. 1, ll. 30-43) – the same configuration as claimed. Moreover, Gonzalez shows this to be the case for its own antibody. Thus, we agree with the Examiner that Gonzalez's teachings would be recognized as generally teaching that PEG extends the half-life of antibodies, regardless of what was stated in its background section (Ans. 17). Appellants have not provided evidence to rebut the Examiner's reasonable findings.

It is not necessary for there to be an explicit suggestion in Barbanti to utilize PEG to enhance the half-life of its antibody. A suggestion, teaching, or motivation to combine the relevant prior art teachings does not have to be found explicitly in the prior art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *Kahn*, 441 F.3d at 987-988. In this case, the Examiner provides a well-reasoned statement for why persons of skill in the art would have had reason to modify Barbanti's antibody with PEG: to extend its serum half-life so more of it will be present to bind to TNF-alpha (Ans. 7), thereby increasing its efficacy. The Examiner also notes that both

IL-8 (Gonzalez) and TNF-alpha (Barbanti) are each involved inflammation and thus the references are in the same field of art (Ans. 7). These are not "conclusory statements" as characterized by Appellants (Reply Br. 6), but statements based on fact and reasoning. The Examiner argues, and we agree, that persons of skill in the art would have recognized the advantages of utilizing PEG upon reading Gonzalez. We are not persuaded by Appellants' that the Examiner's reasoning is flawed.

We do not see any merit in Appellants' argument about single treatments versus multiple treatments (App. Br. 10). In either case, the Examiner's reasoning about improving serum half life of antibody would be applicable. Moreover, the Examiner points to disclosure in Barbanti of single administrations (Ans. 19-20). Thus, we do not see any deficiency in the Examiner's statement of the rejection.

For the foregoing reasons, we affirm the rejections of claims 13 and 14 as obvious over Gonzalez and Barbanti.

CONCLUSION

In summary, we affirm the rejections of claims 1-10, 12, 13, and 15 as obvious over Gonzalez and claims 1, 13, and 14 as obvious over Gonzalez in view of Barbanti. We reverse the rejection of claims 1-10, 12, 13, and 15 as anticipated by Gonzalez.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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